International Journal of Epidemiology
© International Epidemiological Association 1990

Vol. 19, No. 2
Printed in Great Britain

Blood Cadmium in London Civil Servants

J STAESSEN*, W B YEOMAN**, A E FLETCHER*, H L J MARKOWE†, M G MARMOT†, G ROSE‡, A SEMMENCE§, M J SHIPLEY‡ AND C J BULPITT*

Staessen J (Epidemiology Research Unit, Division of Geriatric Medicine, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS, UK), Yeoman W B, Fletcher A E, Markowe H L J, Marmot M G, Rose G, Semmence A, Shipley M J and Bulpitt C J. Blood cadmium in London civil servants. *International Journal of Epidemiology* 1990, **19**: 362–366.

Blood cadmium was measured in 466 randomly selected London civil servants not exposed to heavy metals at work. Blood cadmium ranged from 3.6 to 75.6 nmol/L (0.4 to 8.5 μg/L) with a geometric mean of 6.4 nmol/L (0.7 μg/L) in non-smokers and 13.6 nmol/L (1.5 μg/L) in smokers ($p<0.001$). Blood cadmium was higher in women than in men (9.5 versus 7.8 nmol/L) and was inversely correlated with employment grade ($p<0.001$). The associations with age, body weight and alcohol intake were not significant. After adjusting for gender and the number of cigarettes smoked per day, 36% of the variance of blood cadmium was explained, while the contribution of employment grade was not significant.

There was an unexpected negative relationship between serum creatinine and blood cadmium in men ($r = -0.16$; $p<0.01$). This was not true in women ($r = +0.03$), but the correlation remained present in men after adjustment for age, body mass index and smoking. In contrast, in the two sexes, the correlations between blood pressure and blood cadmium were weak and not statistically significant.

In conclusion, in unexposed subjects, gender and smoking are important determinants of blood cadmium. In addition, a low level of environmental exposure to cadmium is not associated with a deterioration of renal function or an increase in blood pressure.

Cadium is a heavy metal, which during life accumulates in the human body,[1] and which has been implicated in the pathogenesis of renal tubular dysfunction[1] and hypertension.[1,2] In industrialized countries the cadmium burden on the environment showed a rapid growth during the last century, so that cadmium may have important health effects not only via work, but also via environmental exposure.

The present study was conducted in a random sample of civil servants, who were not exposed to heavy metals at work. The aim was to examine the determinants of blood cadmium, and in addition, to investigate whether an association between blood cadmium and serum creatinine and blood pressure could be demonstrated.

METHODS

The civil servants considered in this report were a sample of men and women, drawn from the Department of the Environment Offices in London (The Whitehall, Department of the Environment Study).[3,4] The sample was stratified by age and employment grade, and randomly selected using different sampling fractions in an attempt to provide equal numbers in each age and employment grade group. Employment grade was classified by four levels from one (low) to four (high). Subjects completed a detailed health questionnaire and then came to the clinic for measurement of blood pressure and blood sampling. Systolic and phase V diastolic pressures were measured after the subjects had been lying down for five minutes. A stan-

*Epidemiology Research Unit, Division of Geriatric Medicine, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS, UK.
**The Regional Laboratory for Toxicology, Dudley Road Hospital, Birmingham B18 7QH, UK.
†Department of Community Medicine, University College and Middlesex School of Medicine, 66–72 Gower Street, London WC1E 6EA, UK.
‡Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.
§Current address: Hypertension and Cardiovascular Rehabilitation Unit, Department of Pathophysiology, University of Leuven, Belgium.
Reprint requests to: Dr J. Staessen, Klinisch Laboratorium Hypertensie, UZ Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

Conversion of units
Cadmium: 1 nmol/l = 0.1124 μ/l
Calcium: 1 mmol/l = 4.01 mg/dl
Creatinine: 1 μmol/l = 0.0113 mg/dl
Haemoglobin: 1 mmol/l = 1.605 mg/dl

dard mercury sphygmomanometer was employed and the cuff with an inflatable section of 11 × 25.5 cm was applied to the right arm. Every observer was trained using the London School of Hygiene tapes of auscultatory sounds until they provided reproducible results.

Blood samples were sent to the Wolfson Research Laboratories, Birmingham, for analysis of serum calcium, creatinine and gamma-glutamyltranspeptidase, using a Technicon SMA12 analyser, and to Dudley Road Hospital, Birmingham, for analysis of blood cadmium by atomic absorption spectroscopy.[5] For blood cadmium the intra-assay coefficient of variation ranged from 9.7% at levels below 8 nmol/L (1 μg/L) to 4.0% at concentrations of 89–178 nmol/L (10–20 μg/L). The inter-assay coefficients of variation were of similar magnitude.

Smoking habits were assessed from the health questionnaire. Current smokers were classified by their total reported daily number of pipes, cigars, and hand-rolled or manufactured cigarettes. Light smokers were defined as those consuming less than the equivalent of 10 cigarettes of these smoking materials per day. Moderate smokers had from 10 up to 19 cigarettes per day, and heavy smokers the equivalent of at least 20 cigarettes. Alcohol intake was assessed not only on the basis of the health questionnaire, but also by a three-day dietary recall. The interviews were administered by trained technicians. The correlation of gamma-glutamyltranspeptidase with alcohol intake quantified by questionnaire was 0.20 ($p<0.001$), and by dietary recall 0.18 ($p<0.001$). Subjects were classified as light drinkers if, from both the questionnaire and dietary recall, they appeared to consume less than 25 grams of alcohol per day. They were designated as heavy drinkers, if from the questionnaire or dietary recall they apparently drank more than 50 grams per day. This is approximately equal to 35 units per week, where one unit is defined as half a pint of beer, a single measure of spirits, or a glass of wine. The remaining subjects were considered as moderate drinkers, provided they reported regular alcohol intake.

The distribution of blood cadmium and serum gamma-glutamyltranspeptidase were normalized by a logarithmic transformation. Statistical methods included t-tests for the comparison of means and linear regression analysis. Multiple regression was effected by a step-wise procedure, terminating when all partial regression coefficients were statistically significant at the 5% level.[6]

RESULTS

Determinants of Blood Cadmium

The concentration of blood cadmium in the 466 participants averaged 8.19 nmol/L (0.92 μg/L), ranging from 3.56 to 75.6 nmol/L (0.40 to 8.50 μg/L).

Blood cadmium was higher ($p<0.01$) in women than in men (9.46 versus 7.81 nmol/L; 1.06 versus 0.88 μg/L) and in smokers compared to non-smokers (13.6 versus 6.43 nmol/L; 1.51 versus 0.72 μg/L) (Figure 1). In contrast, the differences between subjects reporting regular alcohol intake and non-drinkers (8.24 versus 8.02 nmol/L; 0.93 versus 0.90 μg/L) and, among non-smokers, between never- and past-smokers (6.44 versus 6.42 nmol/L; 0.72 versus 0.72 μg/L) were not statistically significant. In women, blood cadmium tended to increase with age ($r = +0.12$; $p = 0.18$), so that blood cadmium was higher in post- than in pre-menopausal individuals (10.6 versus 8.5 nmol/L, 1.19 versus 0.95 μg/L; $p = 0.05$) (Figure 1). There was an inverse relationship of blood cadmium with employment grade (men $r = -0.21$; $p<0.001$ and women $r = -0.15$; $p = 0.09$), and a strong positive correlation with the reported number of cigarettes smoked per day (men $r = +0.58$; $p<0.001$ and women $r = +0.53$; $p<0.001$). In contrast, the correlations between blood cadmium and body weight (men $r = +0.02$ and women $r = +0.05$), body mass index (men $r = +0.10$ and women $r = -0.02$), alcohol consumption (men $r = +0.04$ and women $r = +0.01$) and log gamma-glutamyltranspeptidase (men $r = +0.09$ and women $r = +0.08$) were not statistically significant.

In multiple regression analysis, blood cadmium was independently correlated with gender ($p = 0.006$) and with the reported number of cigarettes smoked per day ($p<0.001$), while the partial correlation with employment grade was not statistically significant (t-to-enter = 1.49; $p = 0.14$). The regression equation was: log blood cadmium (nmol/L) = −2.190 + gender (men = 0 and women = 1) + 0.017 number of cigarettes smoked per day. Gender and smoking combined explained 36% of the variance of blood cadmium.

Among male smokers ($n = 109$), 15 only smoked pipes, eight only cigars and 86 only or mainly cigarettes. The geometric mean blood cadmium concentration was 8.02 nmol/L (0.90 μg/L), 7.41 nmol/L (0.83 μg/L) and 15.1 nmol/L (1.70 μg/L) in pipe, cigar and cigarette smokers, respectively. Compared with non-smoking men (6.17 nmol/L, 0.69 μg/L) the blood cadmium concentration was elevated in all three groups, although statistical significance ($p<0.001$) was only achieved with cigarette smoking.

Renal Function and Blood Pressure

The first order correlation coefficients between serum creatinine and log blood cadmium were +0.02 in men,

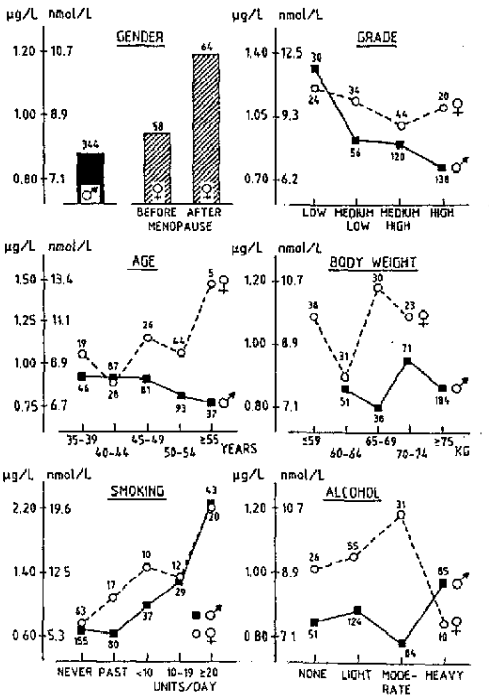

FIGURE 1 *Blood cadmium according to gender and menstrual status, employment grade, age, body weight, smoking habit and alcohol intake in 466 civil servants. For each subgroup the geometric mean and the number of subjects is given.*

+0.03 in women, and +0.03 in the two sexes combined. However, after removal from the analysis of two men with a serum creatinine higher than 180 µmol/L (2 mg/dl), the correlation coefficient was −0.16 ($p = 0.003$) in men and −0.16 ($p<0.001$) in the two sexes together. Serum creatinine was higher in men than in women (91 versus 78 µmol/L; $p<0.001$). The correlation coefficients between serum creatinine and age, body mass index, and the number of cigarettes smoked per day were +0.10 ($p = 0.03$), −0.12 ($p = 0.01$) and +0.11 ($p = 0.03$) in men, and +0.24 ($p = 0.005$), −0.14 ($p = 0.12$) and +0.16 ($p = 0.07$) in women. After adjustment for age, body mass index and smoking, the slope of serum creatinine on log blood cadmium was −6.06 µmol/L/10 $^{nmol/L}$ (95% CI −10.4 to −0.01; $p = 0.05$) in men, and −0.52 µmol/L/10 $^{nmol/L}$ (−4.07 to +10.7; $p = 0.38$) in women.

The single correlations between log blood cadmium and systolic (men $r = +0.03$ and women $r = +0.01$) and diastolic (men $r = +0.03$ and women $r = -0.11$) blood pressures were not statistically significant. Blood pressure was higher in men than in women ($p<0.001$). In men and women, systolic and diastolic blood pressures were significantly and positively correlated with age, body mass index, pulse rate, serum gamma-glutamyltranspeptidase and serum calcium. These covariates explained 16 and 17% of the variance of systolic and diastolic blood pressure, respectively. Also after adjustment for these blood pressure covariates, the relationship of log blood cadmium with systolic and diastolic blood pressure remained weak and was not statistically significant (Figure 2).

DISCUSSION

Blood Cadmium Concentration

The geometric mean concentration of blood cadmium in the present study was 6.4 nmol/L (0.7 µg/L) for non-smokers and 13.6 nmol/L (1.5 µg/L) for current smokers. In subjects who are not exposed to heavy metals at work both the urinary excretion and the blood concentration of cadmium reflect the body burden.[1,7]

In non-smoking individuals, food constitutes the principal environmental source of cadmium.[1] The

TABLE 1 *Clinical and biochemical measurements*

	Men	Women
N	344	122
Systolic pressure (mmHg)	128±17	123±18
	(88–192)	(88–176)
Diastolic pressure (mmHg)	79±13	74±12
	(54–134)	(54–110)
Age (years)	47.9±5.8	47.5±5.7
	(37–58)	(38–57)
Pulse rate (bpm)	70±11	70±10
	(48–108)	(50–92)
Body weight (kg)	76.5±10.3	64.2±8.9
	(50–110.1)	(41.7–102.8)
Body mass index (kg/m^2)	24.6±2.9	24.1±3.2
	(18–35)	18.5–34.5)
Height (cm)	176±7	164±7
	(152–198)	142–180)
Blood cadmium (nmol/L)	9.98±8.22	12.26±11.29
	(3.56–52.5)	(3.56–75.6)
log 10*	0.89±0.29	0.98±0.30
	(7.81)	(9.46)
Serum creatinine (µmol/L)	98±28	78±11
	(66–523)	(53–108)
Serum calcium (mmol/L)	2.41±0.93	2.38±0.87
	(2.18–2.77)	(2.15–2.89)
Gamma-glutamyltranspeptidase (U/L)	16.4±13.2	11.3±10.2
	(4–98)	(4–97)
log 10*	1.14±0.24	0.98±0.21
	(13.7)	(9.5)
Haemoglobin (mmol/L)	9.30±0.69	8.41±0.67
	(6.17–11.15)	(5.86–10.21)

Values are means ± standard deviation with range between parentheses.
*Arithmtic mean ± standard deviation after logarithmic transformation (geometric mean between parentheses).

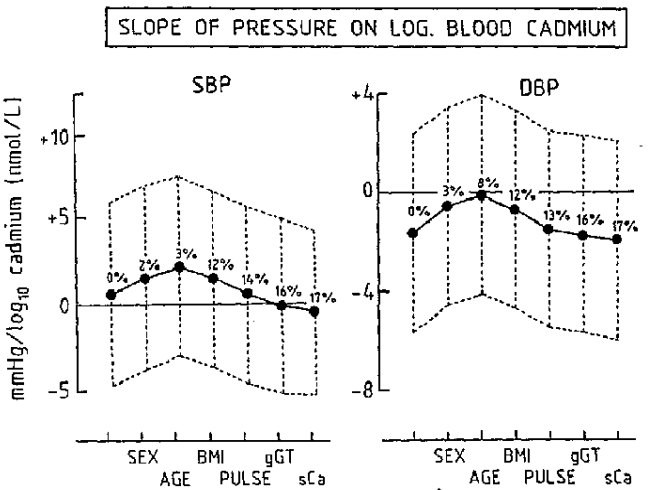

FIGURE 2 *Slope of the relationship between systolic (SBP) and diastolic (DBP) blood pressures and log blood cadmium, unadjusted and after step-wise and cumulative adjustments for sex, age, body mass index, pulse rate, log gamma-glutamyltranspeptidase and serum total calcium. For each adjustment step the 95% confidence interval of the slope and the percentage of explained blood pressure variance are presented.*

daily dietary intake of cadmium shows large variation between individuals, but in most European countries and in the United States averages about 89 to 222 nmol (10 to 25 μg).[8] From 1–7% of ingested cadmium is absorbed.[7] In the general population smoking constitutes a second important source of cadmium exposure. One cigarette contains from 8.9 to 17.8 nmol (1 to 2 μg) cadmium,[8,9] of which approximately 10% may be inhaled by smoking.[8] Much food and many cigarette brands are common to different countries. Accordingly, the average blood cadmium concentration in the present subjects are in agreement with those reported for non-polluted regions in several countries. In a review of blood cadmium measurements in 17 studies performed in three continents and in eight countries, where the dietary intake is between 89 and 178 nmol per day (10 and 20 μg per day), Elinder[8] concluded that non-smokers have a median cadmium concentration in whole blood of the order of 3.56 to 8.92 nmol/L (0.4 to 1.0 μg/L), whereas smokers have a median concentration of 12.5 to 40.0 nmol/L (1.4 to 4.5 μg/L).

Among non-smokers, blood cadmium has been reported to increase with age and to be slightly higher in women than in men.[10] In the present study, the age range was rather small (20 years) and no independent correlation with age was found. In addition, after adjustment for smoking, blood cadmium was almost similar in premenopausal women and in men (Figure 1). Haemoglobin in premenopausal women averaged 8.25 nmol/L (13.2 g/dl) and 9.30 nmol/L (14.9 g/dl) in men. Cadmium in the blood is mainly carried in the erythrocytes and is only transported to a lesser extent in the plasma, where it is bound to albumin and metallothionein.[7] On the other hand, menstruating women often have depleted iron stores and iron deficiency enhances the gastrointestinal absorption of cadmium.[11,12] The latter mechanisms may explain why, in spite of differences in haemoglobin, blood cadmium was nearly similar in men and premenopausal women. Following menopause, blood cadmium was substantially higher than in premenopausal women and men (Figure 1). This was largely due to the high proportion of smokers (71%) among postmenopausal women as compared to premenopausal (43%) and male (46%) participants.

Renal Function and Blood Pressure

The effects of cadmium on health in the general population at the usual level of environmental exposure are unknown. There is a suspicion that environmental cadmium exposure may be related to the development of renal dysfunction and to the pathogenesis of arterial hypertension.[1,13-15]

In the present study there was no correlation between blood cadmium and blood pressure, and even a negative relationship with serum creatinine in men. How this negative relationship should be explained remains to be elucidated. The absence of a relationship

with blood pressure may have been due to the small range of environmental exposure in the civil servants, or to blood cadmium being a less reliable measure of the body burden than urinary cadmium.[1] However, it is also possible that low levels of exposure do not adversely affect renal function and blood pressure. This is now being further investigated in Belgium,[16,17] a country which has a long tradition of non-ferrous industries, and where the general population is being examined in regions with high and with low environmental cadmium contamination.

ACKNOWLEDGEMENTS

The Whitehall (DOE) Study was supported by a grant from the British Heart Foundation. Dr C J Bulpitt is supported by the Xenia Field Foundation. This work was partially supported by the 1987 Merck Sharp and Dohme Travel Grant, awarded by the Belgian Hypertension Committee to Dr J Staessen. The authors also gratefully acknowledge the comments of Dr PMG Broughton, Department of Clinical Chemistry, Wolfson Research Laboratories, Birmingham B15 2TH, UK, and of Prof R Lauwerys and Dr H Roels, Unité de Toxicologie Industrielle et Médecine du Travail, Université Catholique de Louvain, B-1200 Brussels, Belgium.

REFERENCES

[1] Bernard A, Lauwerys R. Cadmium in human population. *Experientia* 1984; **40:** 143–52.

[2] Beevers D G, Cruickshank J K, Yeoman W B, Carter G F, Goldberg A, Moore M R. Blood-lead and cadmium in human hypertension. *J Environ Pathol Toxicol* 1980; **4:** 251–60.

[3] Bulpitt C J, Broughton P M G, Markowe H L J *et al.* The relationship between both sodium and potassium intake and blood pressure in London Civil Servants. A report from the Whitehall Department of Environment Study. *J Chron Dis* 1986; **39:** 211–19.

[4] Markowe H L J, Marmot M G, Shipley M J *et al.* Fibrinogen: a possible link between social class and coronary heart disease. *BMJ* 1985; **291:** 1312–14.

[5] Carter G F, Yeoman W B. Determination of cadmium in blood after destruction of organic material by low temperature ashing. *Analyst* 1980; **105:** 295–7.

[6] SAS/STAT Guide for Personal Computers, Version 6 Edition, SAS Institute, Cary North Carolina, 1987, pp. 877–96.

[7] Nordberg G F, Kjellström T, Nordberg M. *Kinetics and metabolism.* In: Friberg L, Elinder C G, Kjellström T, Nordberg G F (eds). Cadmium and health: a toxicological and epidemiological appraisal. Volume I, Exposure, dose and metabolism. Boca Raton, Florida, CRC Press, 1985, 103–78.

[8] Elinder C G. *Cadmium: uses, occurrences and intake.* In: Friberg L, Elinder C G, Kjellström T, Nordberg G F (eds). Cadmium and health: a toxicological and epidemiological appraisal. Volume I, Dose and metabolism. Boca Raton, Florida, CRC Press, 1985, 23–79.

[9] Elinder C G, Kjellström T, Lind B, Linnman L, Piscator M, Sundstedt K. Cadmium exposure from smoking cigarettes. Variation with time and country where purchased. *Environ Res* 1983; **32:** 220–7.

[10] Elinder C G, Friberg L, Lind B, Jawaid M. Lead and cadmium levels in blood samples from the general population of Sweden. *Environ Res* 1983; **30:** 233–53.

[11] Flanagan P R, McLellan J S, Haist J, Cherian M G, Chamberlain M J, Valberg L S. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. *Gastroenterology* 1978; **74:** 841–6.

[12] Flanagan P R, Haist J, Valberg L S. Comparative effects of iron deficiency induced by bleeding and a low-iron diet on the intestinal absorptive interactions of iron, cobalt, managanese, zinc, lead and cadmium. *J Nutr* 1980; **110:** 1754–63.

[13] Roels H A, Lauwerys R, Buchet J P, Bernard A. Environmental exposure to cadmium and renal function in aged women in three areas of Belgium. *Environ Res* 1981; **24:** 117–30.

[14] Kopp S J, Glonek T, Perry H M Jr, Erlanger M, Perry E F. Cardiovascular actions of cadmium at environmental exposure levels. *Science* 1982; **217:** 837–9.

[15] Staessen J, Bulpitt C J, Roels H *et al.* Urinary cadmium and lead concentrations and their relation to blood pressure in a population with low exposure. *Br J Ind Med* 1984; **41:** 241–8.

[16] Staessen J, Bruaux P, Claeys-Thoreau F *et al.* The relationship between blood pressure and environmental exposure to lead and cadmium in Belgium. *Environ Health Perspect* 1988; **78:** 127–9.

[17] Lauwerys R, Amery A, Bernard A *et al.* Health effects of environmental exposure to cadmium. *Environ Health Perspect* 1989. (In press.)

(Received June 1989)